REMARKS

Upon entry of the amendments presented herein, claims 46-57, 60-64, 66, and 69-126 are pending in this application. Claims 1-41 were previously cancelled, claims 67-68 have been cancelled herein, and claims 42-45, 58-59, and 65 have been withdrawn. Applicants reserve the right to pursue cancelled or withdrawn subject matter, as well as the originally filed claims, in one or more continuing applications. Claims 46-47, 49-52, 55-57, 60, 61, 64, 66, 69 and 70 have been amended, and claims 71-126 have been added. Support for the amendments and new claims is found throughout the specification and in the claims as originally filed. For example, support for the amendment to claim 70 and new dependent claims 71, 73-74, 81-82, 88-89, 95-96, and 122-123 is found at least in paragraphs **[0085]** and **[0086]**. Support for new claims 119-120 is found at least in paragraph **[0084]**, while support for new claims 72, 80, 82, 87, 106 and 121 is found at least in paragraph **[00104]**. Support for amendments to claims 49-52, 55-57 and 61 is found at least in paragraphs **[0050]** and **[0073]** and in the figures as originally filed. Support for new claims 71, 78, 82, 89, 96, 102, 103, 112, 113, 115 and 118 is found at least in paragraph **[0079]**, while support for new claims 101, 111 and 117 is found at least in paragraph **[0082]**. Support for new claims 75-76, 83-85, 90-92, 97-98, 100, 104, 107-108, 116 and 124-126 is found at least in paragraphs **[0031]** and **[0070]** through **[0073]** and in the figures as originally filed. Support for the amendments to independent claims 46, 47, 60, 66 and 69 is found at least in the specification as filed at paragraphs **[0070]** to **[0071]**; **[0072]**, **[0079]** to **[00102]**, and in the figures as originally filed. Accordingly, no new matter has been added by these amendments.

Rejection under 35 U.S.C. §112, 2nd Paragraph

Claims 46-57, 60-64 and 66-70 are rejected under 35 U.S.C. §112, 2nd paragraph, as being indefinite because the term "target partner" is allegedly confusing and unclear as to whether the "target partner" is a receptor, a coenzyme, a cofactor, a substrate, an enzyme, a recruitment protein or a binding partner for the target in an enzyme complex.

Applicants respectfully disagree and submit that the term "target partner" is clearly defined in the specification as a molecule that specifically interacts (*e.g.*, binds) to the target (see *e.g.*, paragraph [0072] at page 17). Accordingly, Applicants maintain that amended claims 46-

57, 60-64 and 66-70 comply with 35 U.S.C. §112, 2nd paragraph, and request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 46-57, 60-64 and 66-70 under 35 U.S.C. § 103(a) as being obvious over Griffin et al. ("Griffin"). The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the negative-positive aptamer selection protocol of Griffin by designating the bound target-target partner/analog complex as the "target molecule" and the unbound target or target partner/analog by itself as the "non target molecule" for the purpose of selecting aptamers that facilitate the complex formation. The Examiner further states that, "Griffin discloses exemplary approaches involving the use of multiple selections to derive aptamers with highly specific properties, as an example, a round of selection involves selecting those oligonucleotides that bind to a complex between a target, thrombin, and a target partner, thrombomodulin." (*See* Griffin col. 24, lines 1-13). Applicants traverse this rejection and the characterizations of the teachings of the Griffin reference.

Amended claims 46, 47, 60, 66, 69 and new claim 114 are directed to methods of identifying an aptamer capable of inducing a change, *e.g.*, a conformational change, in a target upon binding to the target, whereby the change favors association with a target partner, thereby increasing the binding affinity of the target for a target partner relative to the affinity of the target for the target partner where the target is not bound by the aptamer. In contrast to the methods recited by the amended claims, Griffin does not describe or suggest such aptamers and/or any method(s) for identifying such aptamers.

According to the Examiner, "it would have been obvious to add complex-forming target molecules during the selection of aptamers to identify aptamers that bind to the complex. The only modification of the Griffin selection method is to add one more type of molecules that form a complex with the first type of molecules." (Office Action, page 4).

However, neither the instant invention, as recited by the amended claims, nor the Griffin reference itself, is directed to methods of identifying (*i.e.*, selecting) aptamers that recognize complexes of targets. Applicant's invention is directed to methods of identifying aptamers that

act as "agonists" (*see, e.g.*, paragraph **[0070]**), which is referred to as agonist SELEX. The aptamers identified by the Applicant's invention recognize and bind to a target such that, upon binding of the aptamer, the target undergoes a change that increases the ability of the target to bind to its target partner to form a target–target partner complex in the absence of the naturally occurring agonist, if any. These aptamers are not selected for recognition and binding to the target-target partner complex as distinct from the target alone.

The Griffin reference is solely directed to identifying aptamers that bind to the target. There is no disclosure or discussion of aptamers that bind to and induce a change in the bound target of interest. The cited portions of Griffin are equally deficient. Griffin describes a method of identifying aptamers that bind to a target molecule regardless of whether or not it is complexed with another molecule. The Examiner has attempted to characterize the binding of thrombin and thrombomodulin as a target-target partner complex. However, the use of the so called target-target partner complex in Griffin is solely for the purpose of restricting the location on the target of interest to which the aptamer can bind. More specifically, the complex is used in Griffin to ensure that the aptamer binds to the thrombin molecule (the "target") somewhere other than in the region required for the interaction with thrombomodulin so that even with the aptamer bound to thrombin and blocking certain functions of thrombin, the Protein C activity of thrombin is maintained.

Applicants also respectfully disagree with the Examiner's proposed modification of the teachings of Griffin. First, the proposed modification is "inverted" in that, as stated by the Examiner, the modified method of Griffin would not serve Griffin's purposes and it does not lead to Applicant's invention. According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the negative-positive aptamer selection protocol of Griffin by designating the bound target-target partner/analog complex as the "target molecule" and the unbound target or target partner/analog by itself as the "non target molecule" for the purpose of selecting aptamers that facilitate the complex formation. The result of the above-modified Griffin method is an aptamer that binds to either the target or the target partner; in either case in regions other than the location of the target-target partner interaction. There is nothing that even remotely suggest that the resulting aptamers would possess agonist activity. Even where the Examiner's suggested "target molecule" and "non-

targeted molecule" are reversed, the modified Griffin method results simply in an aptamer that binds solely to the target in a region other than the location of the target-target partner interaction. This is not Applicant's claimed invention in either scenario.

Finally, if the target in Griffin were to undergo a change upon binding of the aptamer thereto, the Griffin method would still not lead to the Applicant's invention. Rather, because this modified method would involve toggling between two "different" targets – the unbound and bound version of the target - the result would be an aptamer that recognizes both forms of the target. In other words, this modified method would produce an aptamer that recognizes and binds to a region of the target not involved in change or the interaction of the target with its target partner.

Accordingly, Applicants submit that the methods recited by the amended claims are not rendered obvious by the teachings of the Griffin reference. As such, withdrawal of this rejection is requested.

CONCLUSION

On the basis of the foregoing, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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